Stephen F. Sundlof, DVM, PhD
Director, Center for Veterinary Medicine
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

Dear Dr. Sundlof:

The Centers for Disease Control and Prevention (CDC) strongly supports the approach taken by the Food and Drug Administration (FDA) in the Draft Guidance for Industry "Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-producing Animals," issued in November 1998, and in the "Proposed Framework for Evaluating and Ensuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-producing Animals," issued in December 1998. CDC commends FDA for recognizing the need to consider formally the human safety of the microbial effects of antimicrobial drugs in approving these drugs for use in food-producing animals.

Antimicrobial resistance is a serious emerging problem in the United States and globally and is a key target area in CDC's recently released plan *Preventing Emerging Infectious Diseases: A Strategy for the 21st Century*. Drug-resistant human infections may be acquired in the community, in the health care system, or through the food supply. Although the pathogens acquired in each of these settings are generally different, a common theme is that antimicrobial drug use exerts selective pressure favoring the emergence of resistance. Accordingly, efforts to prolong the useful life of antimicrobial drugs must address drug use in each of these settings.

CDC strongly supports the proposed FDA framework as an important step toward protecting public health while ensuring the availability of antibiotics needed for food-producing animals. If the proposed framework is appropriately implemented, CDC would be more willing to accept the use in animals of antimicrobial drugs that are important in human medicine. CDC is committed to working with FDA and other partners to promote the effective and timely implementation of the framework. Additional comments on the documents are attached.

Sincerely yours,

James M. Hughes, M.D.
Director
National Center for Infectious Diseases

cc:
Dockets Management Branch (HFA-305)

98D-1146

E
C55

Centers for Disease Control and Prevention
National Center for Infectious Diseases

Comments on the Food and Drug Administration's
Draft Guidance for Industry "Evaluation of the Human Health Impact of the
Microbial Effects of Antimicrobial New Animal Drugs Intended for Use
in Food-producing Animals," issued in November 1998, and

"Proposed Framework for Evaluating and Ensuring the Human Safety of the
Microbial Effects of Antimicrobial New Animal Drugs Intended for
Use in Food-producing Animals," issued in December 1998.

General Comments

CDC recognizes that the appropriate use of antibiotics in food-producing animals has important benefits in enhancing animal health and food production. However, there is compelling scientific evidence that use of antibiotics in food-producing animals can lead to adverse public health consequences, due to emergence of resistant bacteria in the animals which can be transmitted to humans through the food supply or direct contact with the animals. Drug resistance in commensal bacteria shared by animals and humans may also develop as a consequence of antibiotic use in food-producing animals and may lead to adverse human health effects. A considerable portion of the evidence is accurately summarized on pages 2-6 of the proposed framework document; additional evidence is soon to be published[1]. In response to the scientific evidence and consistent with recommendations of a World Health Organization consultation in 1997[2], the European Union has prohibited the use of antibiotics used in human medicine -- or selecting for cross resistance to antibiotics used in human medicine-- as animal growth promotants.

The proposed FDA framework provides a mechanism for addressing and resolving a dilemma faced by CDC and others in the public health community whenever an antibiotic is proposed for use in food animals, namely to assess whether approval of the animal drug will compromise the safe and effective treatment of human infections. There are three aspects to the dilemma. First, it is difficult to predict how soon, if ever, and in which pathogens resistance will develop to a drug under conditions of actual use. Antibiotic use "on the farm" is complex and varies by animal species, production system, purpose (therapeutic vs. growth promotion), availability (prescription vs. over the counter), route of administration, label indications, whether off -label use is permitted or prohibited, and other factors. Second, it is difficult to predict the extent to which resistant bacteria or resistance genes that emerge due to animal drug use will be transmitted to humans. Finally, if use of an animal drug leads to resistant human infections, it is difficult under the current regulatory framework for FDA to take mitigating action in a timely manner. In light of these problems and compelling scientific evidence that animal drug use has led to resistant human infections, CDC and others in the public health community have been reluctant to support the approval of antibiotics for animals that have critically important uses in humans.

Under the proposed framework, each drug will be evaluated individually. A critical element will be post-marketing surveillance of resistance to the drug in human domestically-acquired foodborne bacteria as well as further back in the food chain, e.g., from cultures obtained at slaughter. Resistance levels that cross designated thresholds will result in mitigating actions, with withdrawal of the drug from use in one or more species of animals as a last resort. These provisions will be helpful in addressing potential concerns associated with specific drugs, without requiring consensus on the overall issue of human risk due to antibiotic use in food animals that may be impossible to achieve.

Specific Comments

1) The effectiveness of the proposed framework in protecting the public health will depend upon its timely and appropriate implementation. Many details are not specified, e.g., which bacteria will be monitored and which thresholds of resistance or trends of decreasing susceptibility will lead to which mitigating actions. These details are important, as inappropriate specifications could render the entire framework ineffective in protecting the public health. CDC scientists look forward to assisting FDA in the further refinement and implementation of the proposed framework to ensure that the final approach adequately addresses public health concerns. FDA may also wish to seek comment from other sources, including other public health experts, microbiologists, infectious disease clinicians, veterinarians, and the industries affected by regulations. However, it is important to realize that consensus may not be possible and should not be required. Protection of human health should be the primary consideration. To be consistent with the intent of the framework, the outcome of the implementation process must ensure that: 1) the use of class I drugs in food animals is very limited; 2) decreasing drug susceptibility in domestically acquired human enteric bacteria with the same trends in the same bacterial species isolated from animals at slaughter leads rapidly to mitigating actions, including, if necessary, withdrawal of the drug from use in one or more species of animals.

2) In a footnote on page 7, the proposal states that the framework "... as resources permit, will also be used for reviews of existing approved uses of antimicrobials for food producing animals." In fact, it is essential that existing approved uses also be subject to review under this framework. Priority concerns of CDC include review of the current use of fluoroquinolones in poultry and the growth promotants virginiamycin (which selects for cross resistance to the critical human drug quinupristin/dalfopristin), penicillin, and tetracycline.

3) Indicator bacteria that are monitored to identify decreasing drug susceptibility should include foodborne pathogens (e.g., salmonella and campylobacter species) and commensal organisms that colonize both animals and humans and can be pathogenic for humans (e.g., enterococcal species). Mitigating action should be considered when trends of decreasing susceptibility are noted, rather than waiting for full resistance that, once established, may be impossible to reverse. In order to provide reliable data, surveillance of animal isolates at slaughter must be much more extensive than currently performed.

4) CDC agrees that one component of the antimicrobial drug assessment should be the importance of the drug or drug class in human medicine. However, the concept of drug class

should not lead to undue restrictions. For example, if resistance does not occur "class-wide", different drugs within the same class should be able to be classified differently. Similarly, if a drug selects for resistance to a drug from another class, the drug should be classified with the agent of greater importance in human medicine. A drug could be moved from one class to another as new information becomes available, or if its importance in human medicine changes.

5) There should be a separate class (perhaps class 4) for drugs that are not used, or cross resistant to drugs used, in human medicine. These drugs need not be subject to any restrictions related to antimicrobial resistance under this framework. This class would include many growth promotant drugs. This is the cleanest line of division and is consistent with recommendations of World Health Organization consultations that antimicrobials used in human medicine, or which select for resistance to antimicrobials used in human medicine, not be used for growth promotion[3].

6) CDC endorses FDA's statement (framework document, page 17, last paragraph) that more detailed drug sales information (e.g., submitted by state, species, dosage form, season where applicable, calendar year, and containing an estimate of active units sold) should be reported. Drug use data (approximated by sales) are essential for assessment of the selective pressure exerted by drugs, which in turn is critical to better understand surveillance data on drug resistance and for evaluation of measures to mitigate the development of resistance.

7) (page 14, paragraph 3, sentence 4): CDC disagrees with the statement "... generally, it would not appear biologically plausible for resistance to be transferred from animal enteric pathogens to human respiratory pathogens." Identical novel resistance genes have been found in nature in widely divergent genera of animal and human bacteria. Transfer of resistance genes between genera has been documented, although the direction of gene transfer and the frequency of such transfer in the natural setting is not known[4 5 6 7 8]. *Streptococcus pneumoniae*, a human respiratory pathogen causing substantial morbidity and mortality in the United States, readily accepts resistance genes from other bacterial species[9]. Since other species of streptococci are normal inhabitants of the respiratory and gastrointestinal tracts of humans and animals, it is biologically plausible that resistance could be transferred from animal flora through the food supply to *S. pneumoniae* in the human respiratory tract. However, it is much more likely that the emergence and spread of drug resistant *S. pneumoniae* infections in humans has resulted from antibiotic use in humans rather than in animals.

8) CDC strongly endorses FDA's framework approach of classifying antimicrobial drugs according to their importance in treating human infections, regardless of whether these infections are foodborne or have other modes of transmission. This drug classification should be conducted by clinical experts in human infectious diseases. After the drugs have been classified, requirements for pre-approval studies and post marketing surveillance should be determined, taking into account factors such as spectrum of antimicrobial activity and the biologic plausibility and likelihood that resistance may be transferred from animal to human bacterial flora.

1. Smith KE, Besser JM, Hedberg CW, et al. The epidemiology of quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992-1998. N Engl J Med 1999, in press.

2. Anonymous. The Medical Impact of the Use of Antimicrobials in Food Animals. Report and Proceedings of a WHO meeting, Berlin, Germany, 13-17 October 1997.

3. Anonymous. The Medical Impact of the Use of Antimicrobials in Food Animals: Report and Proceedings of a WHO Meeting, Berlin, Germany, 13-17 October 1997.

4. Shoemaker NB, Wang G, Salyers AA. Evidence of transfer of a tetracycline resistance gene between bacteria from the human colon and bacteria from the bovine rumen. Applied Environmental Microbiology 1992;58:1313-20.

5. Trieu-Cuot P, Gerbaud G, Lambert T, Courvalin P. In vivo transfer of genetic information between gram positive and gram negative bacteria. Euro Molec Biol J 1985;4:3583-7.

6. Reysset G, Sebald M. Conjugal transfer of plasmid mediated antibiotic resistance from streptococci to Clostridium acetobutylicum. Ann Inst Pasteur Microbiol 1985; 136B:275-82.

7. Malke H, Holm SE. Expression of streptococcal plasmid determined resistance to erythromycin and lincomycin in Escherichia coli. Mol Gen Genet 1981;184:283-95.

8. Roberts MC, Hillier SL. Genetic basis of tetracycline resistance in urogenital bacteria. Antimicrob Agent Chemother. 1990;34:261-4.

9. McDougal LM, Tenover FC, Lee LN, Rasheed JK, Patterson JE, Jorgensen JH, LeBlanc DJ. Detection of Tn*917*-like sequences within a Tn*916*-like conjugative transposon (Tn3872) in erythromycin-resistant isolates of *Streptococcus pneumoniae*. Antimicrob Agents Chemother. 1998;42:2312-8.